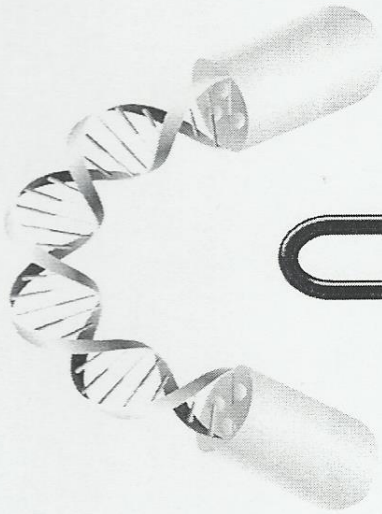


CAPSULE



**apsule**

*Together to cross the 1st pathway*

**SECOND YEAR  
PATHOLOGY  
LECTURE (3)**

**DR. NADIA GALAL**



**CAPSULE**



**CAPSULE TEAM**



**SAHWA FAMILY**

CAPSULE

# بسم الله الرحمن الرحيم

السلام عليكم -- ازيكم ياد كاتره؟ -- يارب تكونوا خير ☺ -- قبل ما نبداً فاضربنا النضارة عاوز أقول ملحوظة صغيرة ← إحنا بنحط الكلام الانجليزي تباع الكتاب عشانه نذاكره -- او غير حد يقرأ العربي بين لأنه ده بيحل ده (يعني العربي يعتبر hint على الكلام الانجليزي ليس أكثر) فاللى هيعد على الكلام العربي بين هيسوع ☺ -- (اللهم بلغت اللهم فاشهد) --- ملحوظة كمانه : إحنا بشر -- يعني لما بنكتب الورقة ممكن نلغبط في اسم ممكن نلغبط في حرف وممكن نيل كلمة مكان كلمة (حاجة طبيعية يعني) عشانه كده بنبقى حاطين الكلام عربى والانجليزي فتمسكش في العربى بس الله يكرمك ☺ ☺

## \* Lecture Content:

المحاضرة جولة  
بس نتعلم بسورت

→ Apoptosis

- Definition
- physiologic
- Pathologic ] types
- morphology of apoptotic cells
- Mechanism of apoptosis
- Comparison betw. Necrosis & apoptosis

→ Gangrene

- Definition
- Types
  - Dry
    - site
    - Causes grossly
  - wet
    - site
    - Causes grossly
  - gas
    - site
    - Causes
- Comparison bet. Dry & wet gangrene

→ IntraCellular accumulation

- Definition
- Types
  - Fatty change
    - Def
    - Causes pathogenesis grossly
  - Pigments
    - Def.
    - Types
      - Microscopic Culture
      - Pathogenesis Causes

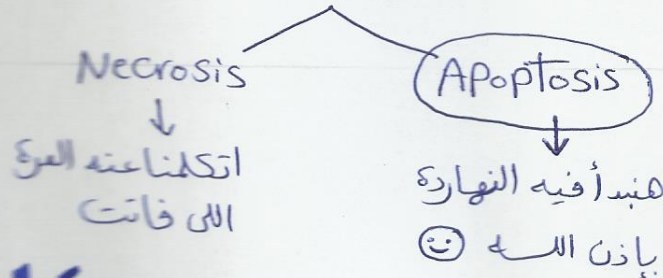
→ Pathologic Calcification

- Def
- Types
  - dystrophic
    - Compare betw. dystrophic & metastatic
  - Metastatic
    - Pathogenesis Causes

→ Cell aging



إلحاقنا إله الخلية لما تعرضت لـ Severe Stimuli بعمل حاجة من الاتساق إما  
irreversible Cell injury (Cell death) أو reversible Cell injury



## \*Definition:

تعالوا نشوف كلام الكتاب :-

### II. Apoptosis (programmed cell death)

It is a form of coordinated and internally programmed cell death.

Apoptosis is a Greek word meaning 'falling off' or 'dropping off'.

- It is a form of cell death which is controlled and regulated by the rate of cell division. When a cell is deprived of growth factors or cell's DNA or proteins are damaged beyond repair, the pathway of cell death (cell suicide) is activated. It is not accompanied by inflammation.
- Apoptosis, is characterized by nuclear dissolution without loss of membrane integrity.

\* فيه تعريف الدكتور كانت كتابه في السلايين منطه برصه :

⇒ Regulated mechanism of Cell death that serves to eliminate unwanted and irreparably (لايسكن إصلاحه) damaged Cells with the least possible host reaction.

⇒ ال Apoptosis نوع من أنواع ال irreversible cell injury وله اسم تاني (Programmed Cell death)

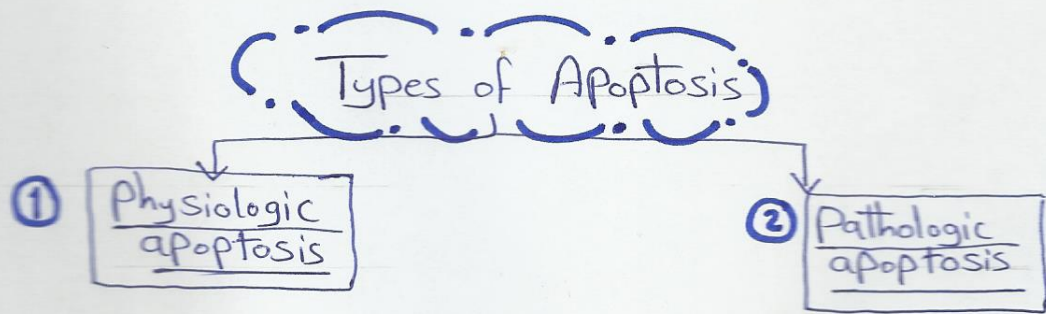
والى بيقرر فيه وبين ال necrosis إنه عدد الخلايا اللى بيحصلها death يكونه خلية واحدة أو

few cells جنب بعض لكن فى ال necrosis كله بيحصل موت بعد أكبر من (الخلايا (death group of cells))

⇒ أهم ما يميز ال Apoptosis ← ① regulation by Certain genes (needs energy) ② active process

③ Could be physiological or pathological ④ Not associated by inflammatory reaction ⑤





## ① Physiologic

### A- Physiologic apoptosis

- The programmed destruction of cells during embryogenesis, as occurs in organogenesis.
- Physiologic involution of cells in hormone-dependent tissues e.g. endometrial shedding, regression of lactating breast after withdrawal of breast-feeding.
- Involution of the thymus in early age.

① زي ما احنا عارفين اير التطور الطبيعي يرتبط بموت خلايا وظهور خلايا وأنسجة جديدة فمثلاً أثناء

تكوين الجنين (embryogenesis) ال organs بتبقى عبارة عن Mass كده بتقوت (يعملها Apoptosis) لغاية لما ال organs تأخذ شكلها النهائي الى الجنين بتولد بيبى (برضه ال Fetus ما بين صوابه بيبقى فيه زوائد جلدية اسمها (interdigital webs) شبه رجل البطة كده فالدم ال الزوائد بيخلصها Removal بال Apoptosis .

② في حالة ال Lactation بعدما الأم تبطل رضاعة ال breast يرجع لحجمه الطبيعي نتيجة ال Apoptosis برضه في حالة ال endometrial shedding (menstruation) بيخلص موت ال cells ال الدم وتنزل مع ال blood .

③ ال Thymus عبارة عن غدة صماء تتكون كبيرة لدى الأطفال وتستمر في النمو طوال سن المراهقة لانه الجسم يتناقص عندما تبدأ الغدد التناسلية بالنضج والإفراز حتى تختفي هذه الغدة في الكبار وهذه العملية تتم بال Apoptosis .



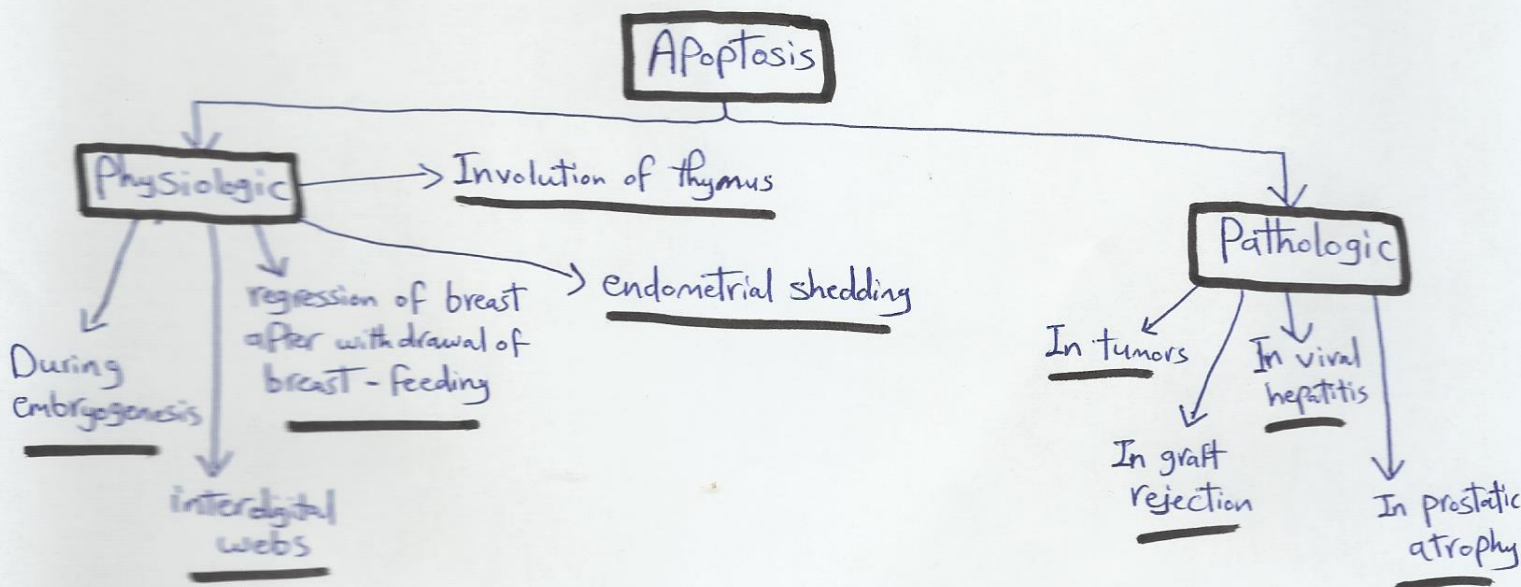
## ② Pathologic:

### B- Pathologic apoptosis

- 1- In tumors exposed to chemotherapeutic agents.
- 2- In graft rejection reactions, by cytotoxic T cells
- 3- In viral hepatitis with formation of Councilman apoptotic bodies.
- 4- In prostatic atrophy after orchiectomy due to hormonal deprivation.
- 5- In radiation and hypoxia.
- 6- In degenerative diseases of CNS e.g. in Alzheimer's disease.

الدكتورة  
مشرقة  
بن ابراهيم  
برفنه

- ① في حالة ان Tumors يتعامل معها باننا ندى المريض Chemotherapeutic agents ودى بتفنى على  
على ان infected cells وبيجى Loss لـ Tumors (يعنى Chemotherapeutic agents بتعمل Apoptosis للورم).
- ② في بعض حالات زرع الأعضاء الجسم يتعامل مع العضو المزروع على أنه جسم غريب وبتأتاك سيهاجم  
بمناعة الجسم بالـ Apoptosis ويموت العضو المزروع ده . (نفس فكرة الـ antigen مع الـ antibody).
- ③ Viral hepatitis بيغل attack على الـ hepatocytes وبيغل Apoptosis وبتتكون الـ apoptotic bodies  
أو بنسجيريا (Councilman bodies).
- ④ سلطات بيغل Cancer في الـ prostate والـ Cancer بيكونه dependent على هرمون التستوستيرون  
فعشانه اعلاج الـ Cancer بشيل الـ prostate أو ممكنه أشيل الـ Testes عشانه (أقرب الـ Cancer cells  
من التستوستيرون فتقت الـ Cancer cells بالـ apoptosis).





# Morphology of apoptotic Cells

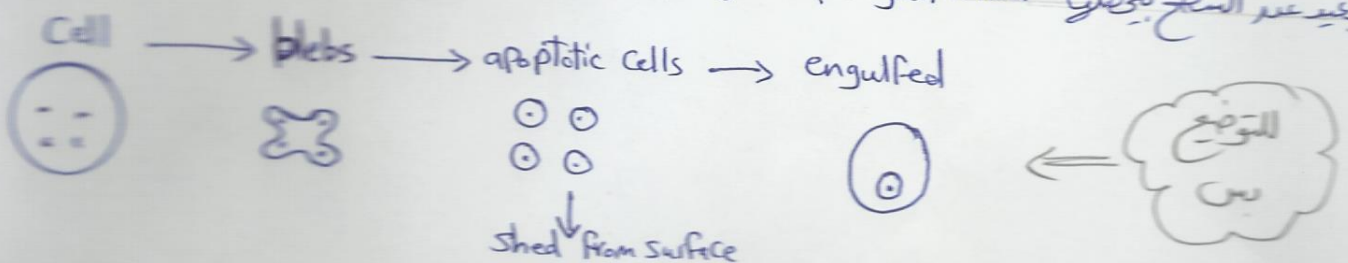
Pathological features: (Fig.2.23). (Morphology of apoptotic cells)

- 1- Death of a single cell or small clusters of cells in the background of viable cells.
- 2- The apoptotic cells are round to oval, with intensely eosinophilic cytoplasm (mummified cells).
- 3- The nuclear chromatin is condensed or fragmented (pyknosis or karyorrhexis).
- 4- The cell membrane may show convolutions or projections on the surface.
- 5- There may be formation of apoptotic bodies containing compact organelles on or around the cell.
- 6- No inflammatory reaction occurs around apoptosis.
- 7- Finally, apoptotic bodies are phagocytosed by macrophages.

← في ال apoptotic cells ال cytoplasm بيقت More eosinophilic وال Cell بيقت Shrinked أو بتقول عليها mummified cells (يعني زي التومياوكة) وال nucleus بيقت Pyknosis ويصيحطت disruption ال Cell membrane بعكس ال necrosis .

← ال Cell membrane بيطلع منه projections وكل حبة سيتوبلازم تأخذ حبة nucleus وتنكسر ال apoptotic cell .  
بس ال Macrophage فتحج على ال apoptotic cells وتعملها phagocytosis، مشانه حبة ميتة ال apoptosis .  
بار Light microscope .

← يعني من الآخر كده: أول خطوة الخلية بتعجز الحجم (shrinked) وبعد كده تبدأ تنكسرت (fragmented) فلو الحيت الصغيرة دي على ال Surface هيطلعها Shedding يعني بخرج ري الجلد كده ولو في organ أو مكانه بعيد عن السطح بيطلعها engulfment بال Macrophages .

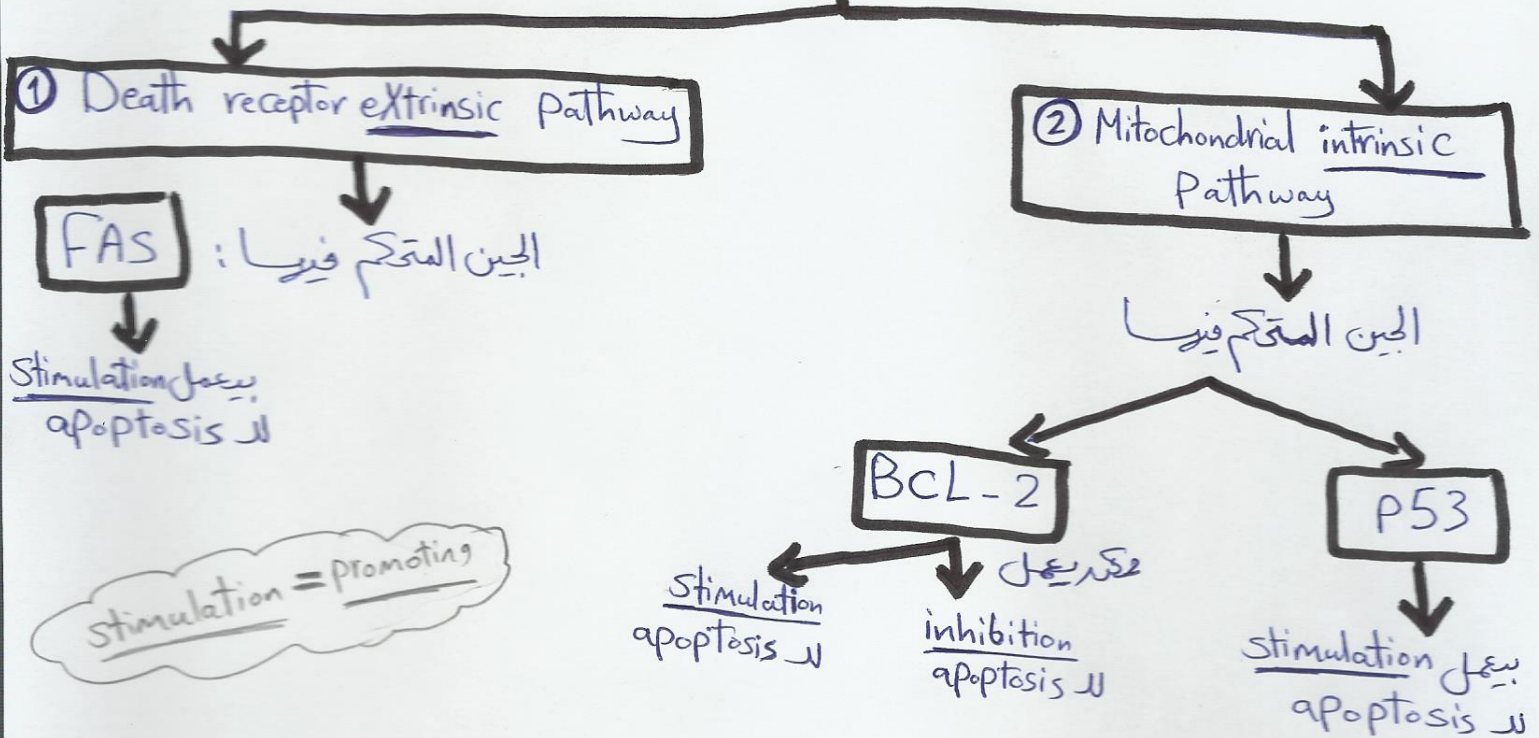




# Mechanism of Apoptosis

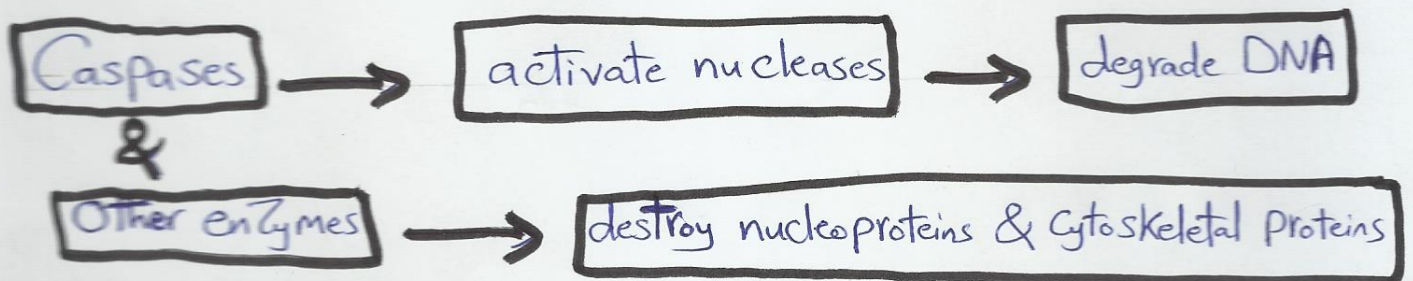
← الدكتور قالت إنه طريقته في الكتاب صعبة نوعاً ما وكالت التي هي عبارة عنه ... تمام؟

\* ال Mechanism عبارة عن خطوتين:



← المرحلة النهائية يعمل activation Caspases لا activate nucleases

وبالتالي يعمل degrade DNA ومع إنزيمات ثانية يعمل destroy nucleoproteins & cytoskeletal proteins



\* برضه إنا حفظ كلام الكتاب للقراءة فقط بين مشاهير تكون عواملين التي علينا 😊



### Mechanisms of apoptosis: (Fig. 2.24)

#### 1. Death receptor extrinsic pathway:

It is triggered through activation of FAS receptor (a member of TNF receptor) Fas-ligand (FasL) is a membrane protein expressed mainly on activated T lymphocytes. When these T cells recognize Fas-expressing targets, Fas linked by the FasL bind caspase-8. Clustering of many caspase molecules leads to their activation, thus initiating the caspase cascade.

#### 2. Mitochondrial intrinsic pathway:

It is triggered by DNA damage e.g. radiation, hypoxia, heat, withdrawal of certain hormones, growth factors and cytokines. These activate members of the Bcl-2 family, which in turn activate pro-apoptotic factors Bax and Bak, causing increased permeability of mitochondrial membrane, and escape of cytochrome *c* into the cytosol. The net result is the activation of the caspase cascade.

- BCL-2 gene family is located in the outer mitochondrial membrane and includes both activators and inhibitors of apoptosis. Thus, it may regulate the apoptotic process by binding to some related proteins (e.g. to *Bax* and *Bak*) for promoting apoptosis, or to *Bcl-x<sub>l</sub>* for inhibiting apoptosis.
- Beside *BCL-2*, the apoptotic pathway is partly also governed by p53 molecule which promotes apoptosis.

## \*Comparison (bet.) Necrosis & Apoptosis

Necrosis	Apoptosis
① Death of group of cells	① Death of individual cells
② Passive process (no energy need)	② Active process (need energy)
③ Elicits inflammatory response	③ No inflammatory response
④ It's always pathologic	④ It may be physiologic or pathologic

\* دی مقارنہ صغیر کہ بین ال necrosis وال Apoptosis لہذا الی حیوة الی جانیہ فی الصغیر جانیہ .



V.V.V.V. Important  
↓

Table 2.1: Difference between Apoptosis and Necrosis		
Feature	Apoptosis	Necrosis
Definition	Programmed and coordinated cell death	Cell death with degradation of tissues by <u>hydrolytic enzymes</u>
Causes	Physiologic and pathologic processes	Pathological, hypoxia, toxins,...
Morphology	1. No inflammatory reaction 2. Death of single cell or small clusters of cells 3. Cell shrinkage 4. Cytoplasmic blebs on membrane 5. Apoptotic bodies 6. Chromatin condensation 7. Phagocytosis of apoptotic bodies by macrophages.	Inflammatory reaction present Death of many adjacent cells Cell swelling initially Membrane disruption Damaged organelles Nuclear disruption Phagocytosis of <u>cell debris</u> by Macrophages
Molecular Changes	1. Lysosomes and other organelles intact 2. Controlled by hormones and enzymes (FAS, BCL-2, p53) stimulation → stim. → inhib.	1. Lysosomal breakdown with liberation of hydrolytic enzymes 2. Cell death by ATP depletion, membrane damage, free radical injury.

تسوية ملحوظات على المقارنة: ① في ال definition بتاع ال Apoptosis ← مكتوب Programmed لأنه في genes  
 بتحكم فيها (وال necrosis ← مكتوب hydrolytic enzymes لأنه ال enzymes بتطلع من ال lysosomes وتعمل digestion  
 ال Content بتاع ال Cell membrane ② في ال Morphology بتاع ال necrosis مكتوب ← Swelling  
 لأنه زي ما قلنا قبل كده إنه نتيجة ال Na Pump Failure بيض ال Na ومعد ال water ويجهل Swelling  
 ③ في ال Morphology بتاع ال necrosis مكتوب Phagocytosis of (Cell debris) ← دي معناها إن الخلية اتكسرت  
 ومبقاش فيها حاجة ④ لأنم نزود في المقارنة إنه ال Apoptosis ← death of single cell  
 وال Necrosis ← death of groups of cells

← وبكده نوكّر خلاصنا ال Apoptosis وفش في موضعين جدد ← Gangrene





الى هي الغرغرينا

# Gangrene

**\* Definition:** Gangrene is necrosis (usually Coagulative) of tissue with superadded putrefaction.

⇒ Types → acc. to amount of blood and tissue fluid in the dead part at time of death → dry, Moist & gas gangrene (من متأكده الجلتري ☺)

← ال gangrene عبارة عن necrosis مبالا infection ب Microorganism مما يؤدي الى تعفن وقيل  
ال necrotic tissues . طب هل لو organ هله gangrene .. هل هتأثر على blood vessel بس ؟ طب  
هل هتأثر على bone بس ؟ .. لا هتأثر على كل المكايم ب b.v. و L.v. و nerves و Connective tissues  
وكله .. تمام .

← ال gangrene بيتقسم حسب المكايم اللى فيه Fluid كتر ولا ايه ؟  
يعني لو Fluid ↓ ← dry ← على الأطراف ، ولو Fluid ↑ ← wet ← فال organs  
وبهذه في نوع ثالث متأخذ اسمه gangrene gas .

## ① Dry Gangrene:

### Types of gangrene:

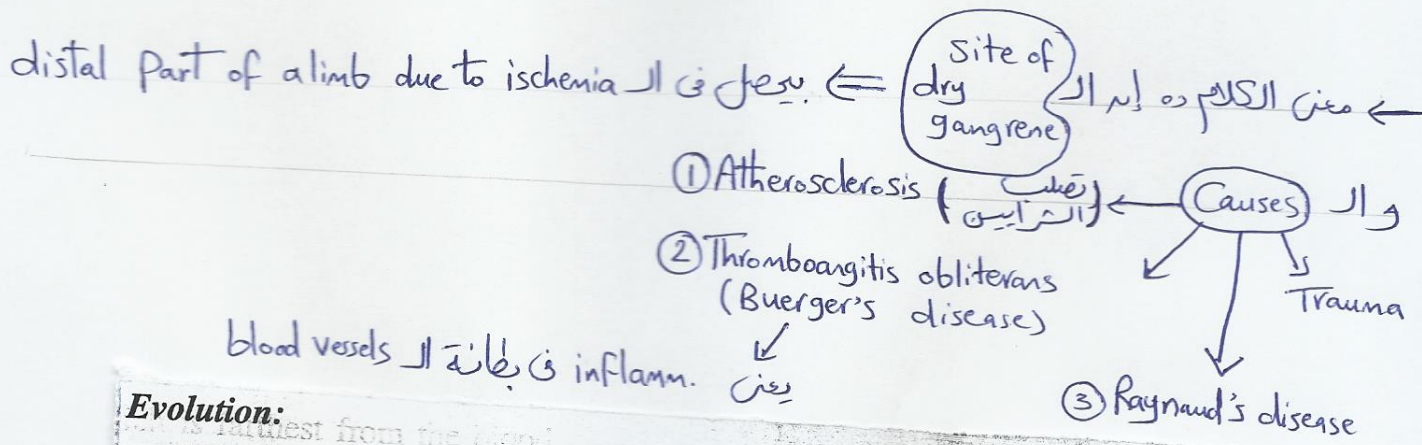
#### I. Dry Gangrene

This form of gangrene begins in the distal part of a limb due to ischemia.

#### Causes of necrosis:

- Atherosclerosis.
- Thromboangitis obliterans (Buerger's disease)
- Raynaud's disease, ergot poisoning
- Trauma





### Evolution:

- It is usually initiated in one of the toes which is farthest from the blood supply.
- The gangrene spreads upwards until it reaches a point where the blood supply is adequate to keep the tissues viable.
- A line of demarcation (zone of acute inflammation) is formed between the gangrenous part and the viable part.

Later on, it becomes a line of separation formed of inflammatory granulation tissue and fibrosis, leading to complete separation of the gangrenous part with falling off, if not surgically removed.

### Grossly:

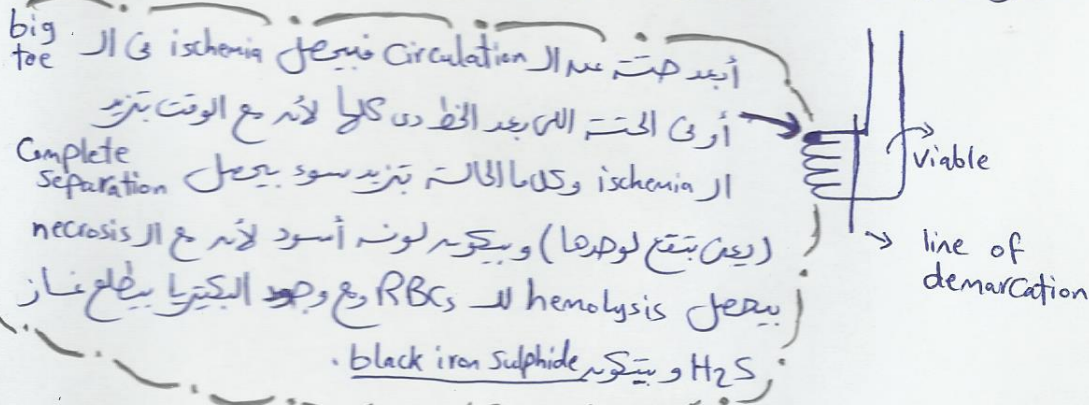
The affected part is dry, shrunken and dark black, resembling the foot of a mummy.

It is black due to liberation of haemoglobin from haemolysed red blood cells which is acted upon by hydrogen disulphide ( $H_2S$ ) produced by bacteria resulting in formation of black iron sulphide (Fig.2.25).

← احنا عارفين إنه الـ blood vessels الـ طالعة من الـ aorta. يطلع منها الـ blood supply لغاية لما توصل لآخر في الرجل الـ big toe (يعني الـ big toe) (بعد حتمه عند الـ Circulation) وبالتالي الـ blood supply هيقف... طب لو المريض عنده Atherosclerosis يعني الحتمه الا بعد هتسح من الـ blood أكثر طبليه؟ لأنه هوصل ischemia (يعني قطع الـ blood supply عن الـ tissue)، طب لما يبقى عندي gangrene احنا قلنا إنه الـ Toes (بعد حتمه عند الـ Circulation) لذلك بتكون Cold و Pale، بعد كده هترفع تاني لو خلاهم سبب obstruction في الـ Venous فالدم هيتجمع في المكان ده والـ surface بتبقى مجعده (Wrinkled)، بعد كده الـ الدم بيقتل الى اسود بسبب تفاعل الـ iron (اللى هو خارج من الـ RBCs النسيه اثر التكررة) مع الـ hydrogen sulphide (اللى الـ  $H_2S$  بيتجه).



بعد كده الجزء الـ necrotic هيفضل يزيل ببطء طر ما يوصل تحت فيرا الـ blood supply فيرا كويس  
 مش هيوصل فيه necrosis يقيم الـ necrosis واقف ويكويه خط فاصل بين الـ necrotic tissue (لون أسود)  
 و الـ normal tissue (الون الطبيعي) اسمها demarcation line وفي النهاية هيوصل auto separation  
 و الـ remaining part (الجزء المتبقى من الـ normal leg) اسمها Stamp وده بيقتل شكله Conical  
 U لآثار الـ blood supply على الأطراف وعلى الـ skin أقل من الوجود في النهن (الـ muscle والـ bone).



## ② Wet Gangrene: (moist gangrene)

### II- Wet (moist) Gangrene:

Wet gangrene occurs in:

1. Naturally moist tissues and organs such as the mouth, lung, intestine, cervix, vulva ..etc.
  2. Intestine commonly due to strangulated hernia, volvulus, intussusception or mesenteric vascular occlusion by thrombosis or embolism (Fig.2.26).
  3. Diabetic foot due to high sugar content in the necrotic tissue which favors growth of bacteria.
  4. Bed sores occurring in a bed-ridden patient due pressure on sites like the sacrum, buttocks and heels (Fig.3.27).
  5. Wet gangrene usually develops rapidly due to blockage of venous, and less commonly, arterial blood flow by a thrombus or an embolus.
- ⊛ The affected part is stuffed with blood which favors the rapid growth of putrefactive bacteria. The toxic products formed by bacteria are absorbed causing profound toxemia and finally death.
  - ⊛ The spreading wet gangrene generally lacks clear-cut line of demarcation.

Grossly: The affected part is soft, swollen, putrified and dark.



← معنى كه انه ال (Site) of wet gangrene في الأماكن التي فيها fluid كثير (Moist tissues)

و organs زي ال (Mouth (Lung (intestine .

← بيحصل في ال intestine نتيجة ل: ① Strangulated hernia (فتق مختنق) ← ال hernia يعني

الفتاد يعني حبة من ال intestine تخرج من ال abdomen wall ويكبر يحصل فيها gangrene

② Volvulus ← يعني الأمعاء تلف هوالين بعضها فالتم هيقف في الحمة دي وطبعاً ال intestine مليانة

بـ nutrients فيجب ال M.O يعني gangrene ③ intussusception ← يعني جزء من الأمعاء يدخل في

التاف (زي لما تقليب الشراب) ④ Mesenteric vascular occlusion (الدكتور مشر هتقوش)

← بيحصل بمرضه في ال Diabetic foot ← مريض السكر عنده ischemia كثير طبياً وعنده ال immunity

ضعيفة فأى M.O ممكن يسبب مشكلته ده غير طبياً ال sugar الكثير اللى في ال tissue -- يعني يقول

لا M.O تعالى أكبر وأثو عندي ⑤

← بيحصل بمرضه ← ال bed sores ← الناس المشلوله بتكونه نائمة على طول فيحصل ال pressure على tissues

وبيحصل قرحة أو gangrene يعني .

## \* ملحوظات :

① المريض اللى عنده gangrene في ال intestine بيقت عنده داء abdominal pain ويبقى سخن وعنده

absolute constipation فالجراغ يفتق ويشيل الحمة اللى فيها gangrene ويحصل الجزأ منه ال viable بيبقى .

⑤ wet gangrene دي بتبقى rapid ليه ؟ -- لأنه قلنا في ال diabetic foot مثلاً بيتقى فيه diabetes

بببساعد على ال bacterial inf. وبالتالي ببساعد على necrosis وفي ال intestine غلبت ال gangrene سريعة

عشان ال blood supply على .

③ مفيش Line of demarcation وكمان مع وجود البكتيريا بتطلع ال toxins ويحصل Toxemia



# ③ Gas Gangrene:

الى قسط  
توده بس الى  
عائز  
في الجزء  
ده

## III-Gas Gangrene:

It is a special form of wet gangrene caused by gas-forming clostridia (gram-positive anerobic bacteria) which gain entry into the tissues:

- ★ Through open contaminated wounds, especially in the muscles, or
- ★ As a complication of operation on colon which normally contains clostridia.
- Clostridia produce various toxins which cause necrosis and oedema locally and are also absorbed producing profound toxemia.

Grossly, the affected part is swollen, edematous, painful and crepitant due to accumulation of gas bubbles within the tissues. Subsequently, the affected tissue becomes dark black with foul smelling, (Fig. 2.28).

← Site ← (wounds ( muscle ( Colon ( Causes ← نوبة  
(gram Positive anerobic bacteria ) gas forming clostridia

V.V.V.V. Important

## \* Comparison (bet.) Dry gangrene & wet gangrene

Feature	Dry Gangrene	Wet Gangrene
Site	Commonly limbs	More common in bowel, lung
Mechanisms	Arterial occlusion	More commonly venous obstruction, less often arterial occlusion
Grossly	Dry, <u>shrunk</u> en and <u>black</u>	<u>Moist</u> , <u>soft</u> , <u>swollen</u> , rotten and dark
Putrefaction (تعفن)	Limited due to very little blood supply	Marked due to stuffing of organ with blood
Line of demarcation	Present at the junction between healthy and gangrenous part	No clear line of demarcation
Bacteria	Bacteria fail to survive	Numerous
Prognosis	Generally <u>better</u> due to <u>little</u> <u>toxemia</u>	Generally poor due to <u>profound</u> <u>toxemia</u>

bowel  
↓  
intestine

عميق  
↓  
Toxemia  
ظاهرة



# Intracellular accumulations

- ① Fatty Change
- ② Pigments

## \* Definition:

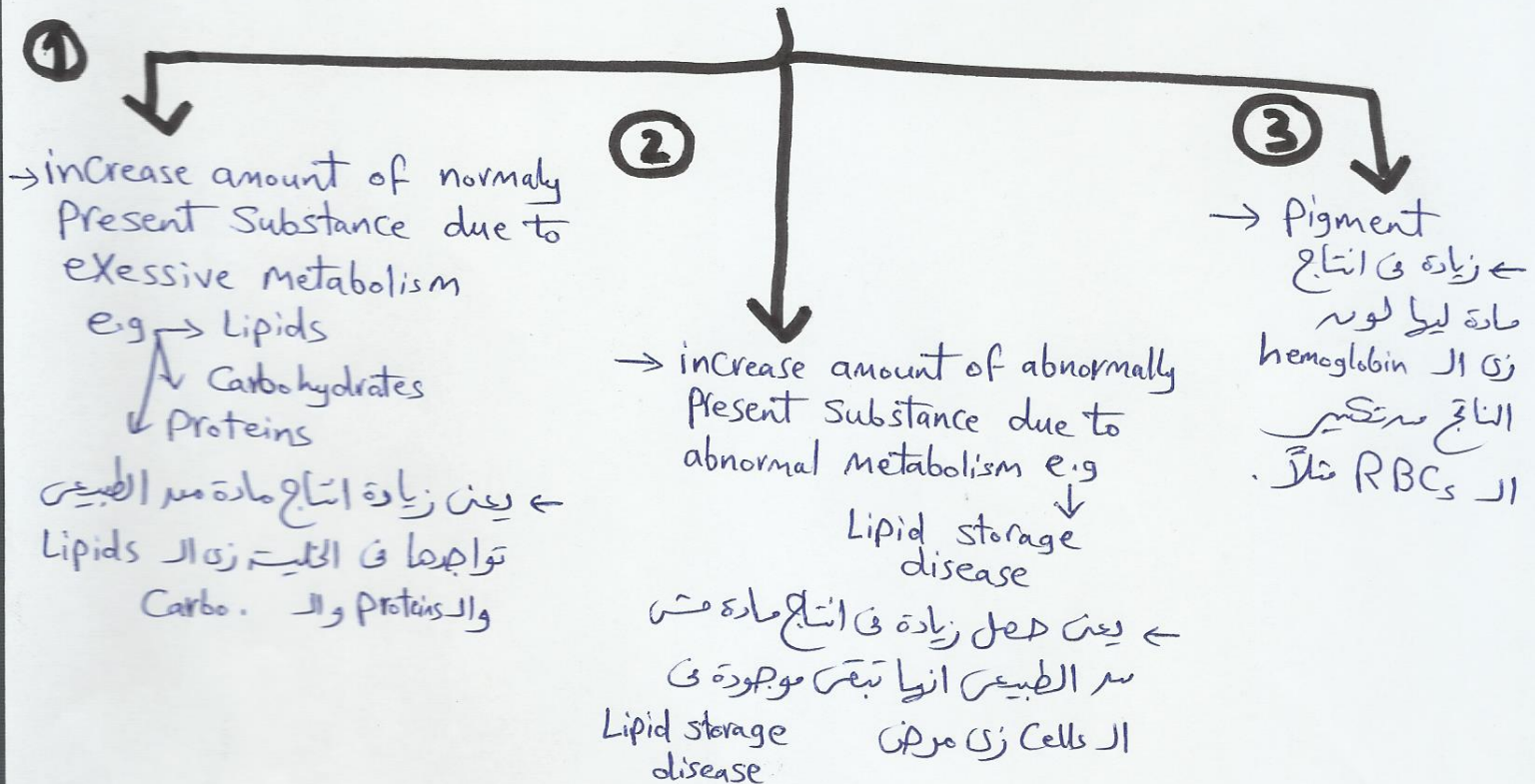
### Intracellular accumulations

Accumulation of substances in abnormal amounts can occur within the cytoplasm (especially lysosomes) or the nucleus of the cell.

Mild intracellular accumulation of the substance causes reversible cell injury while more severe accumulation results in irreversible cell injury.

#### Abnormal intracellular accumulations can be divided into:

- 1- Excessive accumulation of normal cell constituents e.g. accumulations of lipids (fatty acids, cholesterol), proteins and carbohydrates.
- 2- Accumulation of abnormal substances produced as a result of abnormal metabolism due to lack of some enzymes e.g. storage diseases or inborn errors of metabolism.
- 3- Accumulation of pigments e.g. endogenous pigments under special circumstances, and exogenous pigments due to lack of enzymatic mechanisms to degrade these substances or transport them to other sites.





# ① Fatty change : → Def. :

## A- Fatty change (steatosis)

It is the accumulation of neutral fat (triglycerides) within the cytoplasm of parenchymal cells. It is especially common in the liver but may occur in the heart, skeletal muscle and kidneys.

### 1- Fatty liver:

Liver is the commonest site for accumulation of fat because it plays central role in fat metabolism. Depending upon the cause and amount of accumulation, fatty change may be mild and reversible, or severe producing irreversible cell injury and cell death.

← الى يوصف في ال intracellular accu. ← ال Fatty Change في ال Liver والباقى مش علينا .  
← ال Liver ده عضو مهم في ال Fat metabolism عشانه كده أسهل على بيجل فيه accumulation of fat  
فلو ال Fat accu. كمينه بسيطة ال Fatty change فيكون reversible (يعني يتصلح) لكن لو كمينه كبيره  
بيجى irreversible cell injury .

## → Causes:

### Causes of fatty change in the liver:

- Hyperlipidemia, where excess fat reaches the liver exceeding its capacity to metabolize it, as in obesity, diabetes mellitus and congenital hyperlipidemia.
- Alcoholic liver disease (most common).
- Starvation as in protein calorie malnutrition, chronic illness (e.g. tuberculosis), hypoxia (e.g. anemia, congestive heart failure), hepatotoxins (e.g. carbon tetrachloride), drugs (e.g. steroids, methotrexate).

① ← Hyperlipidemia ← لما ال Liver جيل كمينه كبيره مش ال Fat مش هيقدر يتعامل معها وده بيجى مع الناس ال obese أو ال عندها diabetes أو ال عندها Congenital hyperlipid (يعني فيه ناس بتولد عندها abnormal metabolism of lipid) وبالتالي ال level في ال blood بيتجى عالى .  
② ← يعني مثلاً الناس ال بتترب الخمر بيجيلوا تلف في الكبد بسبب ال alcohol وبالتالي يأتوا بدهنية ال Liver في Metabolism of Lipid .



④ (Malnutrition) (سوء التغذية) ← ال protein هيقول ... طب ايه العلاقة بين ال protein وال Lipids

ايفانقلنا انه ال Free fatty acid يدخل ال Liver ويدخل معاه ال glycerol وبتحولوا ال triglycerides  
أهو ال triglycerides ده ميعرفش يمشى فى الدم إلا لو كانه ماسك فى ال protein فلو ال protein ده قل  
ال triglycerides هتتجمع فى ال Liver (accumulation) فى حالة ال (hypoxia) ← الدم  
مبيوصلش ال Liver كويس فمبقتش يقوم بوظيفته فى حالة ال (hepatotoxins) ← بيجعل تسمم ال Liver

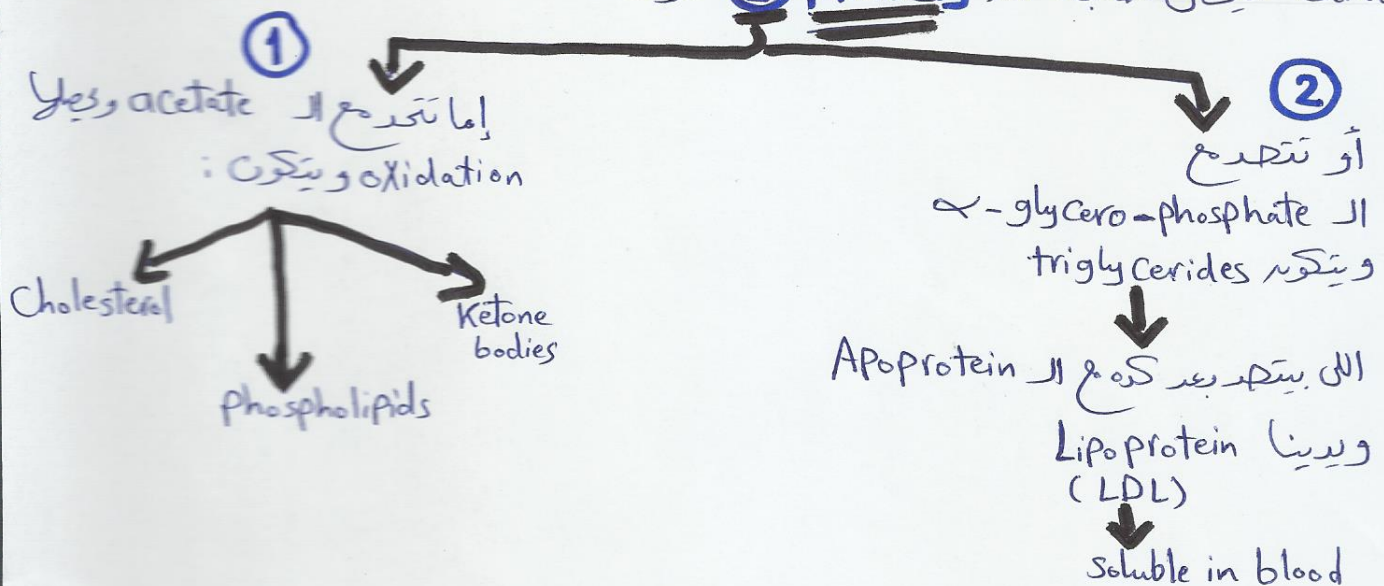
\*notes:

- \* Free fatty acid  $\xrightarrow{\text{oxidation}}$  Keton bodies
- \* Free fatty acid + glycerol  $\rightarrow$  Triglycerides (insoluble in blood)
- \* Triglycerides + protein  $\rightarrow$  Lipoprotein (LDL) (Soluble in blood)

## ⇒ Pathogenesis of fatty Liver : ( Lipid Metabolism in Liver )

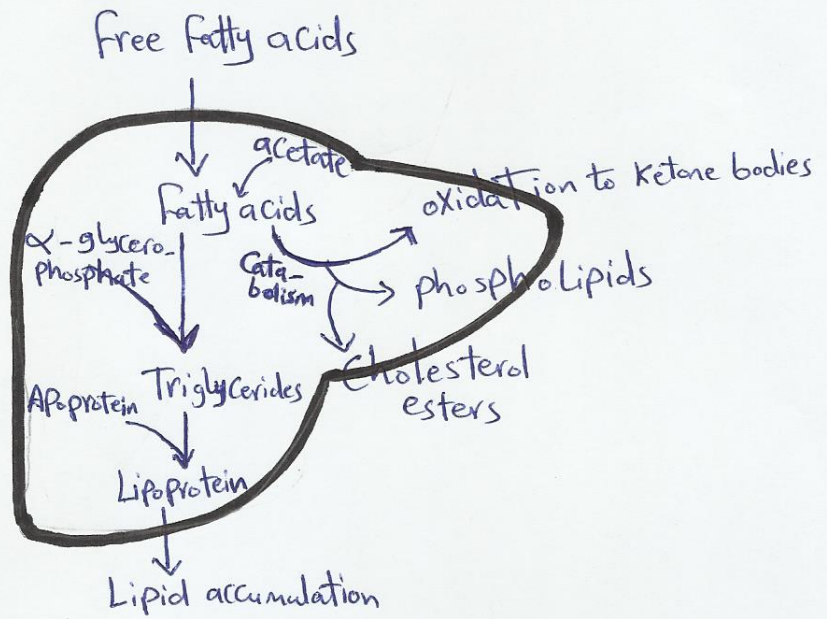
ال المفروض انه ال Free fatty acid فى ال Circulation بتخس على ال Liver فلو حصل معاه ال Metabolism

أو ال Catabolism هيجعل حاجة من ال ② Pathway دول :





ده diagram  
که نشان می‌دهد  
ماشین از آن



\* طب لو جینا علی ای حتمه فی ال pathway ده و جعل فیها خلل می‌شود ای . accu لا Fat فی ال Liver :

① یعنی لو وصلتی oxidative لا Fatty acid (یعنی ال pathway الاول اتقفل) هیزید ال pathway التای و هیزید انتاج ال Triglycerides .

② لو زاد ال alpha-glycerophosphate هیزید تصنیع ال Triglycerides .

③ لو قل ال Apoprotein هیزیل ال Lipoprotein و هیزید ال Triglycerides .

\* و طبیبائی کل الحالات الی فانت زیاده ال Triglyceride می‌شودی لتراکم ال Fat فی ال Liver .

\* و ده کلام ال کتاب :

- ☞ Decreased oxidation of fatty acids into ketone bodies resulting in increased esterification of fatty acids to triglycerides.
  - ☞ Increased  $\alpha$ -glycerophosphate causing increased esterification of fatty acids to triglycerides.
  - ☞ Decreased synthesis of lipid acceptor protein resulting in decreased formation of lipoprotein from triglycerides.
  - ☞ Block in the excretion of lipoproteins from the liver into plasma.
- Liver cell damage occurs, when fat cannot be metabolized in it.
- In most cases of fatty liver, one of the above mechanisms is operating, while in case of liver injury by chronic alcoholism nearly all the factors are implicated.



# \* Morphology Features:

→ Grossly: - Size → enlarged (accumulation of fat)

- Consistency → Soft - edge → rounded

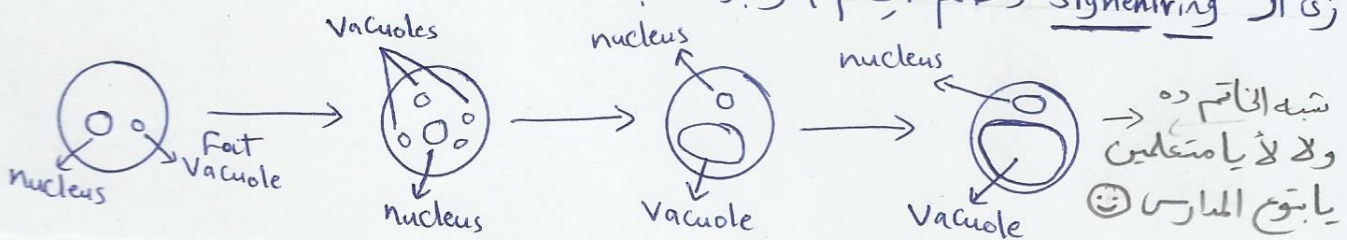
- Cut surface → bulging , yellow , greasy

Liver لهما اظهر اقطع حبة مرار  
ar edges بتاعته فتخرج ليرة  
(المفروضه في الطبيعي اننا ننقل  
مكارنا).

→ Microscopic picture:

→ Clear vacuoles ← \* وأنا بفر العينة عناه أفصل وقت الميكروسكوب باستعمل alcohol  
وده يسوب ar Fat فلو خلايا ar Liver مليات Fat فتسبب مكارنا

في ال Liver cells تبقى Swollen بال Fat وال Fat ده موجود في vacuoles عدد هاجير وبدره  
تتجمع في vacuole واحدة - ال vacuole دي تضغط على ال nucleuses لحد ما يبقى شكل الخلية  
زي ال Signet ring (خاتم الختم) وبدره بقى ال Cell يضل رapture وتوت .



- The vacuoles are initially small and are present around the nucleus (**microvesicular**).
- With progression of the process, the vacuoles become larger pushing the nucleus to the periphery of the cells which becomes flattened giving signet ring appearance (**macrovesicular**).
- At times, the hepatocytes laden with large lipid vacuoles may rupture and lipid vacuoles coalesce to form **fatty cysts**.
- Infrequently, **lipogranulomas** may appear consisting of collections of lymphocytes, macrophages, and some multinucleated giant cells.
- Fat can be demonstrated in fresh unfixed tissue by frozen section followed by fat stains such as Sudan dyes (Sudan III, IV, Sudan black), oil red O and osmic acid.

وده كلام  
الكتاب



## ② Pigments :

### Pigments

Pigments are colored substances that are either exogenous, coming from outside the body, or endogenous, sensitized within the body itself, (Table 2.3).

Table: 2.3 Types of pigments	
<b>A-Endogenous pigments</b>	تحدث بسبب داخل الجسم ←
1-Melanin 2-Haemoprotein-derived pigments (Haemosiderin) 3-Lipofuscin (wear and tear pigment)	
<b>B-Exogenous pigments</b>	تحدث أو يتغير من خارج الجسم ←
1-Inhaled pigments (Carbon) 2-Injected pigments (Tattooing)	

\* الدكتور قالت ده بين اللي مطلوب منها في ال Pigments نعرف ال  
 def. الجيوب ده (Types)

① endogenous ← أتا عندي في الجسم ① Melanin ← اللي بيدى لون الشعر والجلد  
 ② haemoprotein ← ودي عبارة عن ال hemoglobin الناتج من تكبير RBC ③ Lipofuscin  
 أو بنسبها (wear & tear pigment) ← مع ال aging بيحصل atrophy في ال heart يعني القلب بيضعف  
 في الحجم وكمان بيحصل accu. ال pigment اسمها Lipofuscin ودي نتيجة ال Metabolism بتاع الخلايا  
 اللي بتتكرر في الخلايا ومبتقدرش تتخلص منها فبتتجمع في ال lysosome وتعمل yellowish brown pigment  
 ويكثر بتجمع في ال neurons ويكثر في ال Liver cells.

② exogenous ← ① Inhaled pigments (Carbon) ← طبعا إيه ال inhal.  
 لعوام السيارات والوقود وكل ده بيخل ال وسيل فلو أنت بصيت على ال وسيل بتأخذ واحد طبيعي فتلاقي  
 ال Cut section بتأخذها أسود نتيجة ال Carbon اللي بتعمل inhalation وده اسمه anthracosis.  
 ② Injected pigments ← الوشم أو التاتو .



# Pathologic Calcification

→ Def. :

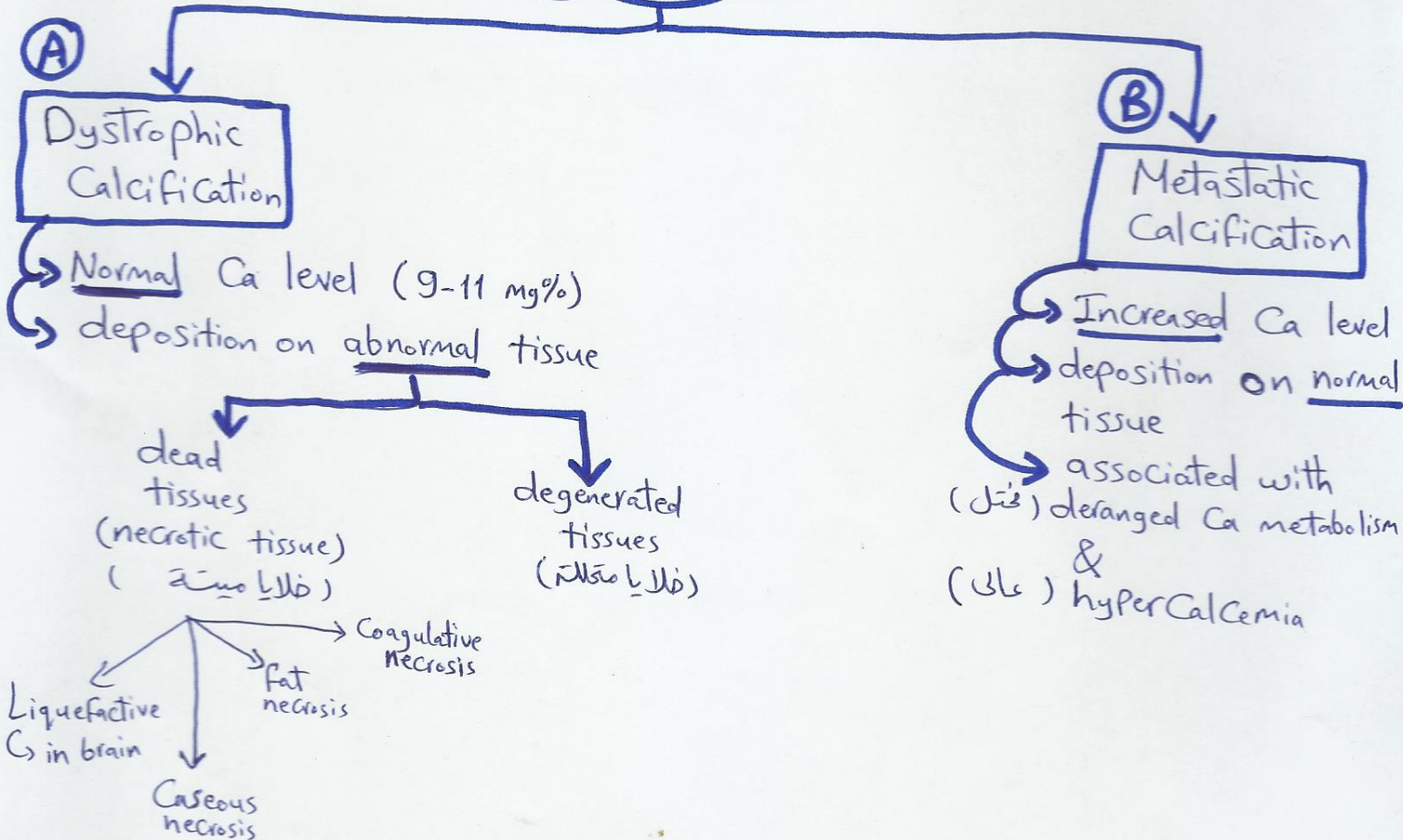
## Pathologic calcification

Deposition of calcium salts in tissues other than osteoid or enamel is called pathologic or heterotopic calcification.

**Histologically:** Calcium salts appear as deeply basophilic intra or extracellular, irregular and granular clumps. Occasionally, heterotopic bone formation (ossification) may occur.

← الـ Ca المروجن طبيعي موجود في الـ osteoid (enamel) teeth bone  
في حالة تانية غير الـ osteoid، يحصل Pathologic Calcification  
فلما ترسب الـ Ca

## \* Types





# Ⓐ Dystrophic :

## → Causes:

Causes:

### A- Calcification in dead tissue:

1. Caseous necrosis in tuberculosis, liquefactive necrosis in chronic abscess, fat necrosis following acute pancreatitis or traumatic fat necrosis in the breast and coagulative necrosis in infarction.
2. Thrombi in veins producing phleboliths.
3. Haematomas.
4. Calcification in breast cancer detected by mammography.
5. Dead parasites like in hydatid cyst and schistosoma eggs.

\* الدكتورة  
مترجمة  
كل اجنا  
منشع الى  
من شرج

### B- Calcification in degenerated tissues:

1. Dense old scars may undergo hyaline degeneration and subsequent calcification.
2. Atheroma in the aorta and coronaries.
3. Monckeberg's sclerosis shows calcification in the tunica media of muscular arteries in elderly people (Fig.2.34).
4. Stroma of tumors as uterine fibroids.
5. Some tumors show characteristic spherules of calcification called psammoma bodies (Fig.2.35), such as in meningioma, papillary serous cystadenocarcinoma of the ovary and papillary carcinoma of the thyroid gland.

in dead tissue ← ① tissue يمكن موتى بأى حاجة زى ال infection أو toxins أو حتى cut

فى ال B.S. بـ فمثلاً dead tissue زى ال Caseation (necrosis بتاع ال T.B.) أو زى ال Coagulative necrosis (بسبب cut blood supply) يعنى به الآخر زى necrosis يمكن يخل فيه Calcification.

⑤ Thrombi أو haematomas ← لو واحد اتخبط بيخل جمع دموى.

③ فى ال Breast Cancer بنحضره بنوع سر الأشعة اسمها mammography فالراجل الى بيعمل الأشعة دي بيخاف لما يلاقى فيه لوه أبيض ناصع (deposition of Ca) لأن ممكن يكون Cancer فى ال breast.

④ ال dead parasites زى bilharzial ova (تبقّر موجودة فى ال bladder أو ال intestine) وزى ال hydatid cyst (تبقّر موجودة فى ال Muscle).

in degenerated tissue ← الى حى مش necrotic يعنى لو أنا عنيت old scar بتاعت أن جمع

ممكن يخل فيه Calcification أو ممكن يخل فى تصلب الشرايين.



## → Pathogenesis:

Denatured proteins in necrotic or degenerated tissue bind phosphate → that binds Ca → Ca phosphate

## ③ Metastatic:

### → Causes:

#### Causes:

##### **A- Excessive mobilization of calcium from the bone:**

1. Hyperparathyroidism (e.g., parathyroid adenoma, parathyroid hyperplasia or chronic renal failure) or production of parathyroid hormone-related protein by some malignant tumors.
2. Bony destructive lesions, such as multiple myeloma and metastatic carcinoma.
3. Prolonged immobilization of a patient results in disuse atrophy of the bones and hypercalcemia.

##### **B- Excessive absorption of calcium from the gut:**

1. Hypervitaminosis D
2. Milk-alkali syndrome caused by excessive oral intake of calcium in the form of milk and administration of calcium carbonate in the treatment of peptic ulcer.

##### **C. Vitamin D related disorders including:** Vitamin D intoxication and sarcoidosis (in which macrophages activate vitamin D precursor).

Parathyroid hormone

Parathyroid ← hyperparathyroidism ① ← Excessive Mobilization of Ca (A)

وهو مسئول عن الـ Ca metabolism في الـ body فلو فيه hyperplasia في الـ gland فالـ hormone الـ

عالي وبالتالي الـ Ca level في الـ blood فيحصل deposition الـ Ca في الـ normal tissues .

② لو حصل Metastatic tumor وصل الـ bone فحصل تكسر الـ bone فحصل الـ Ca ويوصل الـ blood .

③ immobilization ← قلت الحركة يحصل deposition of Ca .

① زي ما إله عارفه الـ Vit. D بيعمل absorption الـ Ca فالتالي

الـ يتأخذ Vit D كتر يحصل الـ excess absorp. الـ Ca في الـ intestine وبالتالي الـ Ca level



⑤ الناس الى عندها Peptic ulcer يشربوا اللبن بكثره عشان يعادلوا حامضية المعدة ولان اللبن

فيه Ca كثير (٣)

⑥ Vit. D related disorders ← Sarcoidosis ← يبقى فيه excess absorp. لـ Ca شدة إنه

فيه active لـ vit D

\* ملحوظة: Metastatic Calcification: عكس يعمل في الـ (Kidneys, Lungs, Stomach, arterial walls)

- Joint Capsule

## → Pathogenesis:

→ Inorganic phosphate binds with Ca ions → Calcium phosphate.

V.V.V. Important

## (\* Comparison (bet.) Dystrophic & Metastatic Calcification)

Table 2.4: Differences between Dystrophic and Metastatic calcification		
Feature	Dystrophic calcification	Metastatic calcification
Definition	Deposits of calcium salts in dead and <u>degenerated tissues</u>	Deposits of calcium salts in <u>normal tissues</u>
Calcium metabolism	<u>Normal</u>	<u>Deranged</u>
Serum calcium level	<u>Normal</u>	<u>Hypercalcemia</u>
Causes	<ul style="list-style-type: none"> <li>-Necrosis (caseous, liquefactive, fat, coagulative)</li> <li>-Thrombi, hematoma.</li> <li>-Dead parasites, old scars</li> <li>-Atheroma,</li> <li>-Monckberg's sclerosis</li> <li>-Certain tumors</li> </ul>	<ul style="list-style-type: none"> <li>-Hyperparathyroidism</li> <li>-Bony destructive lesions</li> <li>-Prolonged immobilization</li> <li>-Hypervitaminosis D</li> <li>-Milk-alkali syndrome</li> <li>-Sarcoidosis</li> </ul>
Pathogenesis	Increased binding of phosphates with <u>necrotic and degenerated tissue</u> , which in turn binds to calcium forming calcium phosphate precipitates.	Increased precipitates of calcium phosphate <u>at certain sites</u> due to hypercalcemia e.g. in <u>kidneys, lungs, stomach, arteries, synovium.</u>



# Cellular aging

↓  
الدكتورة قالت علي مش مهم ومش مقلق  
بس قالت قراءة بعض للمعرفة ليس أكثر  
وأنا فزكت عن كدة صغرة كده ☺

← متوسط عمر الأفراد يعتمد على كذا Factor :

- ① في جينات بتحكم في كده (Intrinsic genetic Process) ② environmental factors زي radiation والتلوث (عوامل السيارات وغيرها) ③ Lifestyle زي مثلاً التدخين وشرب الكحوليات بيسرع من عليـ
- ال aging ④ Age related diseases زي ischemic heart (diabetes (hypertension

## Cellular bases of aging

### ① Decreased Cellular replication

زي ما إحنا عارفين إنه الخلية لما عدد معين من الانقسامات (65) وبعد ما تقوت طبعاً ليه ؟ --- لأنه ال telomeres (نويات الكروموسومات) بيصغروا Progressive shortening  
طبعاً المشكلة بكون بتحل بإنزيم ال telomerase  
بس لو الإنزيم ده مش موجود المشكلة مش  
متصلح ويحدث ال Aging

### ② Oxidative stress (Free radical)

طبعاً ال Free radical  
بيحدث مع ال Aging ويبيكر  
ال Mitochondria وال DNA  
ومده ثم بيصل Cell damage  
لذلك ينصح بأكل الأطعمة الملونة  
فاكهة خضروات  
لأنها تحتوي على antioxidant اللي بتحمي  
الجسم من ال Free radicals

← طيب كده المحاضرة خلاصت ناقص بس شوية أسئلة

من فهمتم ال Cases الی الدكتور عرضتكم ☺☺



# Questions :-

## \* MCQ:

- ① Apoptosis is characterized by (a) always Pathologic (b) active Process (c) surrounded by inflammatory Rx (d) affect group of cells } **ans (b)**
- ② Fatty change of liver may follow any of the following conditions except:  
 a) Diabetes mellitus b) Congestive heart failure } c) starvation  
 d) F.B. e) chronic alcoholism **ans (d)**
- ③ Organ discoloration in brown atrophy is attributed to:  
 A) lipochrome pigment B) Lipofuscin pigment c) bile pigment  
 D) Carbon pigment e) Hemosiderin pigment **ans (b)**
- ④ Endogenous body pigments include all of the following except:  
 A) hemosiderin B) Melanin c) Lipofuscin d) Lipochrome **ans (d)**
- ⑤ A good example of dystrophic Calcification is:  
 A) Haematomas b) renal Calculus c) gall stones  
 D) Ca deposition in kidney in hyperparathyroidism **ans (A)**
- ⑥ Dystrophic Calcification occurs in all of the following except:  
 A) primary hyperparathyroidism B) Atheromatous plaque D) hydatid cyst  
 D) Dead bilharzial ova **ans (A)**
- ⑦ Apoptosis is a type of reversible cell injury (X)
- ⑧ Fatty Change is accumulation of triglycerides within parenchymal cells (✓)



## \* Cases:

(26)

① Upper GI endoscopy is performed on a 43 year old man who has complained of heartburn with a substernal or upper epigastric burning pain following meals for several years. Biopsies are taken of an erythematous area of the mucosa seen in the lower esophagus located 3 cm above the gastroesophageal junction. There is no lesion, no ulceration, and no hemorrhage noted. The biopsies demonstrate the presence of columnar epithelium with goblet cells. These findings are most consistent with:

- A) acute inflammation      B) Epithelial hyperplasia      C) Metastatic carcinoma  
D) ischemic injury      E) Epithelial Metaplasia      ans (E)

② A 59 year old female had loss of consciousness for over an hour. When she became arousable, she could not speak and she could not move her right arm or leg. A cerebral angiogram revealed an occlusion to her left middle cerebral artery. Months later, a computed tomographic (CT) scan shows a large 5 cm cystic area in her left parietal lobe cortex. The CT finding demonstrates a lesion that is the consequence of resolution from which of the following events:

- A) Liquefactive necrosis      B) Atrophy      C) Coagulative necrosis  
D) Caseous necrosis      E) Apoptosis      ans (A)

③ Following the birth of her first child, a 19-year-old female begins breast feeding the baby. She continues breast feeding for almost a year with no difficulties and no complications. Which of the following processes that occurred in the breast during pregnancy allowed her to nurse the infant:

- A) stromal hypertrophy      B) Epithelial dysplasia      C) Steatocyte atrophy  
D) Ductal epithelial metaplasia      E) Lobular hyperplasia      ans (E)



4) The light brown perinuclear pigment seen on H&E staining of the cardiac muscle fibers in the grossly normal appearing heart of an 80 year old male at autopsy is :

ans B

- A) Hemosiderin resulting from iron overload
- B) Lipofuscin from (wear & tear)
- C) Glycogen resulting from a storage disease
- D) Cholesterol as a consequence of atherosclerosis
- E) Calcium deposition following necrosis

5) Cellular apoptosis, with loss of single cells, plays a significant role in the histopathologic appearance of :

- A) Viral hepatitis
- B) Brown atrophy of the heart
- C) renal transplant rejection
- D) Chronic alcoholic liver disease
- E) Barbiturate overdose

ans A  
ans C



بہن بچہل اکثری حالت ال renal transplant rejection  
لا تہ قابل فی السؤال کلمہ significant یعنی  
الاجابہ ہی ans C

## \* Essay :

1) Define : apoptosis - gangrene - intracellular accumulations - Fatty change - Pigments - Pathologic Calcification

2) Compare bet. : 1) Necrosis & apoptosis , 2) Dry & wet gangrene

3) Dystrophic & metastatic Calcification .

3) Mention : Mechanism of apoptosis - examples of physiologic apoptosis

طبعاً الأستاذ المقالة کثیر فی الحاضر دی فیکسوا انتوا بقى بن الدكتور  
آکف لہ امتیازہ المستقیم جای MCQ بن طبعاً ال essay فیکر بن فوال Final

# تمجد الله

# Capsule ..